24. (Amended) The method of claim 1, wherein said expression construct is delivered by direct intratumoral injection.

REMARKS

I. Status of the Claims

Claims 1 and 6-26 are pending in the application. Claims 10-17 are withdrawn from consideration as directed to a nonelected invention. Claims 1, 6-9, and 18-26 stand rejected under 35 U.S.C. §112, second paragraph. Claims 1, 6-9, and 18-26 stand rejected under 35 U.S.C. §112, first paragraph. Claims 1, 7-9, and 18-20 stand rejected under 35 U.S.C. §102(a) as being anticipated by either Gjerset, *Molecular Carcinogenesis,* 14:275-285 (1995) or Roth, (WO 95/28947). Claims 1, 6-9, 18-21 and 23-26 stand rejected under 35 U.S.C. §103(a) as being unpatentable over either Gjerset, *Cancer Gene Therapy*, 1:330, Abstract V-87 (1994) or Gjerset, *Proceedings of the American Association for Cancer Research*, 36:21, Abstract 123 (1995) in view of Zhang, *Cancer Gene Therapy*, 1:5-13 (1994). The specific grounds for rejection, and the applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1, 6-9, and 18-26 are rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants have amended the claims as suggested by the Examiner. Reconsideration and withdrawal of the rejection is respectfully requested.

III. **Rejection Under 35 U.S.C. §112, First Paragraph**

Claims 1, 6-9, and 18-26 are rejected as lacking an enabling disclosure. The Examiner states that the claims encompass gene therapy for the treatment of cancer *in vivo*, and due to the unpredictability in the art, the teaching and working examples provided, and the breadth of the claims, it would require undue experimentation to practice the invention. Applicants respectfully traverse.

Applicants point out that the PTO is required to assume that the specification complies with the enablement provisions of §112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24 (CCPA. 1971). The Examiner cites Smith, *Annu. Rev. Microbiol.*, 49:807-838 (1995) (hereinafter Smith) for the proposition that there are numerous problems associated with gene therapy. Specifically, the Examiner identifies problems associated with cell targeting, entry of DNA into cells, expression of useful levels of gene product over an appropriate period, avoidance of the host immune response, and the destruction of treated cells. Smith addresses the alleged clinical effectiveness of gene therapy as a whole. It is inappropriate to apply the short-comings of the entire gene therapy field to the instant invention without considering the parameters that enable the invention as described by the specification.

Characteristics inherent in the present invention address many of the Examiner's concerns regarding gene therapy. For example, one embodiment of the present invention is the adenoviral delivery of the nucleic acid encoding p53. Smith teaches that adenoviral vectors have been successfully administered to a remarkable number of animal tissues *in vivo*, and that initial expression levels are generally robust (see page 828, last complete paragraph, and the paragraph bridging pages 828-829). The transient nature of adenoviral expression does not hinder the

effectiveness of the present invention due to the fact that expression of p53 protein need only be transient to induce apoptosis, thus leading to a therapeutic effect. Additionally, the propensity of some adenovirus vectors to illicit an immune response can be advantageous in the destruction of cancer cells (see Smith at page 829, fourth complete paragraph). Smith concludes that rapid progress has been made in the application of viral vectors for gene therapy, particularly in cancer applications (page 831, first full paragraph).

The Examiner also alleges that *in vitro* cell culture models are poor predictors of the *in vivo* efficacy of cancer therapeutics. The Examiner cites Dermer, *Bio/Technology*, 12:320 (1994) (hereinafter Dermer) in support of this proposition. Applicants respectfully point out that Dermer is an opinion piece that makes numerous conclusory statements that are unsupported by references to any research articles. In fact, i*n vitro* studies are accepted by those with ordinary skill in the art of gene therapy and pharmacology as being reasonably predictive of success. The Court of Appeals for the Federal Circuit has stated:

> *In vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with respect to the particular pharmacological activity are generally predictive in *in vivo* test results, i.e., there is a reasonable correlation there-between. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed. Cir. 1985). Thus, applicants assert that the cell culture examples described in the specification are reasonably predictive of *in vivo* efficacy.

Applicants submit the declaration of Deborah R. Wilson, the Associate Vice President of Clinical Research at Introgen Therapeutics ("Introgen") as evidence that the rejected claims are enabled (Appendix C). Dr. Wilson's declaration sets forth the numerous clinical trials, involving Introgen's INGN 201 adenovirus-p53 composition, which is disclosed in the specification of the present application, that are underway or have recently been completed or that have been

approved. The declaration also sets forth a number of clinical trials that have employed another adenoviral p53 construct, Schering Plough's SCH 58500 adenovirus-p53 construct.

Applicants point to the U.S. Patent and Trademark Office's own training guide, albeit on utility instead of enablement, which states, "[A]s a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility." Because the requirements for utility and enablement are intertwined, Applicants contend that the submission of bountiful clinical trial evidence strongly weighs against a rejection for enablement.

Adenovirus-p53 is being tested against a number of cancers. INGN 201 is currently in phase III clinical trials for head and neck cancer. Phase II clinical trials are underway or have been completed for head and neck cancer, non-small cell lung carcinoma, breast cancer, and esophageal cancer. INGN 201 was used or has been approved for phase I clinical trials for lung cancer, breast cancer, liver cancer, glioma, prostate cancer, bladder cancer, colorectal cancer, malignant ascites, head and neck cancer, and solid tumors from a variety of origins. Additionally, several clinical trials have been conducted for various cancers including ovarian cancer, lung cancer, bladder cancer, and metastatic colorectal cancer using a different Ad-p53 construct from another company, Schering Plough. The clinical trial evidence shows that Ad-p53 is safe and has potentially useful clinical activity. This evidence further indicates that administration of Ad-p53 is achieved regionally, intravenously, directly, intraperitoneally, and intravesically. The Declaration of Deborah R. Wilson confirms the enablement of the claimed invention. Applicants respectfully request the rejection of all the claims for lack of enablement be withdrawn in view of the foregoing reasons.

IV. Rejection Under 35 U.S.C. §102(a)

Claims 1, 7-9, and 18-20 are rejected under 35 U.S.C.§102(a) as being anticipated by either Gjerset, *Molecular Carcinogenesis* 14:275-285 (1995) or Roth, (WO 95/28947). Applicants respectfully traverse.

The claimed invention is drawn to a method for the induction of p53-mediated apoptosis in a cell comprising the steps of (a) introducing into said cell an expression construct comprising a nucleic acid segment encoding p53 and a promoter operably linked to said nucleic acid segment, and (b) contacting said cell with at least one ***inhibitory agent that inhibits DNA repair.*** In contrast, the references cited by the Examiner teach the use of ***DNA-damaging agents.***

A DNA-damaging agent is any chemical compound or treatment method that ***induces DNA damage*** when applied to a cell. For example, alkylating agents, such as nitrosurea, cisplatin, busulfan, and chlorambucil, damage DNA by reacting with nucleophiles in the DNA molecule. Intercalating agents, which insert between the planar base-pair structure of the DNA double helix, are another class of chemical compounds that damage DNA. Various forms of radiation are also well known for their ability to cause DNA lesions. For example, ultraviolet radiation causes the dimerization of adjacent pyrimidines. X-rays and gamma rays induce breaks in the phosphodiester backbone of DNA and cause DNA-DNA and DNA-protein crosslinking.

In contrast, an agent that inhibits DNA repair ***functions by interfering with a cell's ability to recognize and/or repair damaged DNA***. There are numerous inhibitors of DNA repair known in the art (for a review see Martin, *Journal of Photochemistry and Photobiology*, 63:162-70 (2001) (hereinafter Martin)). One well-known target for DNA-repair inhibitors is poly(ADP-ribose) polymerase-1 (PARP-1) (see Martin at page 163-64). PARP-1 is an enzyme involved in the base-excision repair pathway. Several PARP-1 inhibitors are known that impair the

enzyme's function by competing with NAD^+ at the catalytic domain. It has been demonstrated that the use of PARP-1 inhibitors, such as 3-aminobenzamide and 4-amino-1,8-naphthalamide, result in increased sensitivity to DNA damage. (see Martin at page 164). In summary, an inhibitory agent does not create lesions in the DNA, but rather impairs the cell's ability to repair existing damage in its DNA.

It would be evident to one of ordinary skill in the art that inhibiting DNA repair and causing DNA damage are distinct processes. Moreover, the specification distinguishes inhibitors of DNA repair from DNA-damaging agents (see specification at p. 12, ln. 25 through p. 14, ln. 21; p. 48, ln. 21 through p. 49, ln. 6). The claims must be construed in light of the specification and "the description may act as a sort of dictionary, which explains the invention and may define terms used in the claims." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*aff'd*, 517 U.S. 370).

It is black letter law that an anticipatory reference must disclose each and every element of the claimed invention. The references cited by the Examiner do not disclose an agent that inhibits DNA repair. Without such disclosure, the rejection must fail. Reconsideration and withdrawal of the rejection is respectfully requested.

V. Rejection Under 35 U.S.C. §103(a)

Claims 1, 6-9, 18-21, and 23-26 are rejected under 35 U.S.C. §103(a) as being unpatentable over either Gjerset, *Cancer Gene Therapy*, 1:330, Abstract V-87 (1994) (hereinafter Gjerset 1994) or Gjerset, *Proceedings of the American Association for Cancer Research*, 36:21, Abstract 123 (1995) (hereinafter Gjerset 1995) in view of Zhang, *Cancer Gene Therapy*, 1:5-13 (1994) (hereinafter Zhang).

Gjerset 1994 or Gjerset 1995 are said to teach a method for induction of p53-mediated apoptosis in a glioblastoma cell comprising introducing into the cell via gene transfer the wild-type p53 gene and contacting the cell with either cisplatin or gamma radiation. Zhang is said to teach that E1-deficient adenoviral vectors with a CMV promoter are efficient means for gene transfer and high-level expression of wild-type p53 protein in human lung cancer cells. Thus, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the adenoviral vector disclosed by Zhang as an efficient means of gene transfer of the wild-type p53 gene to a cell in the method taught by either Gjerset 1994 or Gjerset 1995. Applicants respectfully traverse.

The claimed invention is drawn to a method for the induction of p53-mediated apoptosis in a cell comprising the steps of (a) introducing into said cell an expression construct comprising a nucleic acid segment encoding p53 and a promoter operably linked to said nucleic acid segment, and (b) contacting said cell with at least one ***inhibitory agent that inhibits DNA repair.***

As acknowledged by the Examiner, none of Gjerset 1994, Gjerset 1995, or Zhang disclose the administration of ***an inhibitory agent of DNA repair.*** Gjerset 1994 and Gjerset 1995 teach the contacting of a cell with ***DNA-damaging agents***, namely cisplatin and gamma radiation. Cisplatin and gamma radiation are specifically defined as DNA-damaging agents in the present specification (see specification at p. 48, ln. 21 through p. 49, ln. 6). The claims must be construed in light of the specification. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*aff'd*, 517 U.S. 370).

Furthermore, it would be evident to one of ordinary skill in the art that inhibiting DNA repair and causing DNA damage are distinct processes. A DNA-damaging agent is any chemical compound or treatment method that ***induces DNA damage*** when applied to a cell. For example,

alkylating agents, such as nitrosurea, cisplatin, busulfan, and chlorambucil, damage DNA by reacting with nucleophiles in the DNA molecule. Intercalating agents, which insert between the planar base-pair structure of the DNA double helix, are another class of chemical compounds that damage DNA. Various forms of radiation are also well known for their ability to cause DNA lesions. For example, ultraviolet radiation causes the dimerization of adjacent pyrimidines. X-rays and gamma rays induce breaks in the phosphodiester backbone of DNA and cause DNA-DNA and DNA-protein crosslinking.

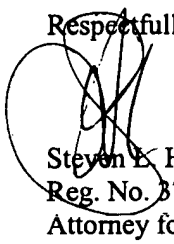
In contrast, an agent that inhibits DNA repair ***functions by interfering with a cell's ability to recognize and/or repair damaged DNA***. There are numerous inhibitors of DNA repair known in the art. One well-known target for DNA-repair inhibitors is poly(ADP-ribose) polymerase-1 (PARP-1) (see Martin at page 163-64). PARP-1 is an enzyme involved in the base-excision repair pathway. Several PARP-1 inhibitors are known that impair the enzyme's function by competing with NAD^+ at the catalytic domain. It has been demonstrated that the use of PARP-1 inhibitors, such as 3-aminobenzamide and 4-amino-1,8-naphthalamide, result in increased sensitivity to DNA damage. (see Martin at page 164). In summary, an inhibitory agent does not create lesions in the DNA, but rather impairs the cell's ability to repair existing damage in its DNA.

It is black letter law that the cited references must, in combination, disclose each and every element of the claimed invention. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). The references cited by the Examiner do not disclose an agent that inhibits DNA repair. Without such disclosure, the rejection must fail. Reconsideration and withdrawal of the rejection is respectfully requested.

VI. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Examiner Brumback is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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APPENDIX A: MARKED UP COPY OF CLAIMS

1. (Amended) A method for the induction of p53-mediated apoptosis in a cell comprising the steps of (a) introducing into said cell an expression construct comprising a nucleic acid segment encoding p53 and a promoter operably linked to said nucleic acid segment, and (b) contacting [a] said cell with at least one inhibitory agent that inhibits DNA repair.

9. (Amended) The method of claim [4] 1, wherein said promoter is a cytomegalovirus CMV promoter.

21. (Amended) The method of claim [1] 18, wherein said tumor cell is in a subject.

22. (Amended) The method of claim [1] 21, wherein said subject is human.

23. (Amended) The method of claim [1] 21, wherein said inhibitory agent is delivered by direct intratumoral injection.

24. (Amended) The method of claim 1 [2], wherein said [stimulatory agent] expression construct is delivered by direct intratumoral injection.